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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/851,422	05/09/2001	Xianxhang Yu	035879-0122	2132

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/19/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/851,422	YU ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2002 and 27 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *6,7 and 10-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I (species amoebapore) in Paper No. 11 is acknowledged. The traversal is on the ground(s) that searching for all of the claims would not put serious burden on the Office. This is not found persuasive because the restricted groups are drawn to different inventions for reason of record and searching all of the pending claims would put serious burden on the examiner for reason of record. As for applicant's request for rejoining of method under in re Ochiai. the method with all of the limitation of allowable product will be rejoined when the product is allowable.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6, and 7 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant says at line 1 of page 10 in Paper No. 11 that claim 7 reads on the elected species but claim 7 is peptide from non-elected species, i.e., melittin, therefore being withdrawn from further consideration. Claims 10-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a invention, there being no allowable generic or linking claim Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Claims 1-19 are pending and claims 1-5, 8, and 9 are examined as they are drawn the elected species, amoebapore. When the elected species is allowable, the search will be expanded to see if the generic claim is allowable.

Claim Objections

Claims 3- 5 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 3-5 depend on claim 1 drawn to a peptide containing modification of epsilon carbon of lysine residue. However, the peptides in claims 3- 5 are also drawn to native peptides and/or other amoebapore without the necessary modification specified in claim 1.

Claim 8 is objected to because of the following informalities: claim 8 has not been amended to reflect the election of species. Claim 8 contains a peptide derived from a non-elected species. Appropriate correction is required.

Specification

The disclosure at paragraph [0071] is objected to because of the following informalities: the side chain of lysine has missing $2CH_2$.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 lists "amoebapore...and analogs and derivative thereof" but it is not clear what is the difference between analogs, and derivative thereof, and the rest of species in claim 3.

Claim 4 recites "amoebapores, amoebopore analogs and amoebopore deriavatives" but it is not clear what the metes and bounds are for the limitations. What is the differences between the three? For this office, the Office will assume that "amebapores" and "amoebopore analogs" are unmodified R groups in SEQ ID NO:1 shown in claim 5 and "derivatives" are one or more R groups of the lysines are modified. However, this treatment does not relieve applicant the burden of responding to this rejection.

Claim 5 recites the limitation "the adjacent lysine"" in 4. There is insufficient antecedent basis for this limitation in the claim.

Claim 5 is confusing because it is not clear how the R of group of each of the lysine residue is modified. For the purpose of the this office action, the Office will assume that claim 5 is drawn to unmodified SEQ ID NO:1, one, two, or all of the three

lysine residues are modified. However, this treatment does not relieve the applicant the burden of responding to this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3-5 are rejected under 35 U.S.C. 102(b) as being anticipated by either Leippe et al (A5 of IDS, Paper No. 15, 1994, Proc. Natl. Acad. Sci. USA, vol. 91, pages 2602-2606) and Andra et al (A6 of IDS, Paper No. 15, 1996, FEBS Letters, vol. 385, pages 96-100).

The claims are interpreted as unmodified epsilon amino group of the three lysines in the instant SEQ ID NO:1 shown in the instant claim 5. Leippe et al teach at Fig. 1 that H3 is identical to the unmodified instant SEQ ID NO:1 and further teach the amebopore peptide has pore-forming and cytotoxic activities. Note Table 1, Figs 3-5. Andra et al also teach at Fig. 1 that H3 (top row) is identical to the unmodified instant SEQ ID NO:1 and also teach the amebopore peptide has pore-forming and cytotoxic activities. Note Figs. 2, 4, and Table 1. Thus, either, Leipe et al or Andra et al teach the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Leippe et al or Andra et al as applied to claims 3-5 above, and further in view of Pinto et al (A11 of IDS, Paper No. 15, 1999, The Prostate Journal, vol. 1, pages 15-

26), WO 97/33908 (A2 of IDS, Paper No. 15, 1997), and Liu et al (1979, Endocrinology, vol. 104, pages 962-966, abstract only).

This rejection is based on the Office interpretation of the claimed invention as the first product in claim 8, i.e., amoebapore H3 domain modified by linking two gamma linked glutamates through epsilon group of the C-terminal lysine. The primary references teach the amoebapore H3 domain peptide backbone (identical to the unmodified instant SEQ ID NO:1 shown in claim 5) is a cytotoxic peptide and further teach the positive charge at the C-terminal end, especially having lysine residue is important for the peptide's biological activity. Note for example the paragraph bridging page 2606-5, and right column at page 2603 of Leippe et al. WO 97/33908 teaches at page 3 line 15 to page 4 line 5 that there are great interest to use lytic peptides in the art (the primary references teaches that amoebapore H3 domain is a lytic peptide, see at page 2604 and Fig. 5) for cancer treatment but the use of such lytic peptides in cancer treatment has been limited because the peptides are also toxic to normal cells as well as target cells and teaches the need for inactivating the lytic peptides until they reach the target cells. The references cited so far does not teach why one skilled in the art would connect the gamma-linked di-glutamates to epsilon residue of the C-terminal residue of the cytotoxic peptide taught by the primary references. However, Pinto et al teach at pages 22 and 23 that poly-gamma glutamates removing activity of PSMA, highly expressed in prostate cancer has been used to target anti-cancer agents specifically to prostate cancers thereby minimizing damaging to normal. Liu et al are cited to show that peptide bond between polyglutamate to another peptide via epsilon group of lysine amino acid is well known technique in the art. Since Pinto et al suggest that gamma linked polyglutamates could protect normal cells from cytotoxic drugs by inactivating them until they reach the right place, and di-glutamates are a minimum requirement of poly-glutamates and perhaps easiest and cheapest to make if works, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make procytotoxin comprising amoebapore H3 domain modified by linking two gamma linked glutamates through epsilon group of the C-terminal lysine in order to inactivate the cytotoxic amoebapore H3 domain until it reaches target cells,

namely prostate cancer cells expressing PSMA which cleaves the gamma linked glutamates and selectively kills prostate cancer cells instead of causing havoc to entire body of the person who has prostate cancer. The state of art is such that making the product (amoebapore H3 domain modified by linking two gamma linked glutamates through epsilon group of the C-terminal lysine) is accomplished with a reasonable expectation of success.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 8, and 9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 12, 13, and 21 of copending Application No. 09/938,623. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant base claim is drawn to procytotoxin comprising cytotoxic peptide bound to something via peptide bond between epsilon group of lysine residue of said cytotoxic peptide to said something while the base claim of the co-pending application is also drawn to a procytotoxin comprising cytotoxic peptide bound to something via peptide bond susceptible to cleavage by protease, but the base claims of co-pending application does not say that the susceptible to cleavage could be peptide bond through epsilon group of lysine residue, however the dependent claim 7 says that one species of base claim

could be peptide bond between epsilon of lysine and something. Further instant claims define the structural nature of something connected to epsilon group of lysine while the co-pending application functional nature of something, i.e., protease cleavable moiety (function). However, the at least the elected species diglutamates is protease (more specifically PSMA) cleavable moiety. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
May 13, 2003

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800 1600